Remarks

Reconsideration of the subject application is respectfully requested. Claims 1, 3-9, 12-18, 20-22, 24-29, 32, 33, 35-37, 40-48, 50-52, 54-59 and 62-71 are pending. The Examiner has indicated that claim 34 is pending and has included that claim in the list of rejected claims. Claim 34 was, however, canceled by the previous amendment. Therefore, Applicants do not include claim 34 in the list of rejected claims.

Rejection of claims 1, 3-9, 12-18, 20-22, 24-29, 32, 33, 35-37, 40-48, 50-52, 54-59 and 62-71 under 35 U.S.C. §103(a) over U.S. Patent No. 6,277,391 to Seo et al. in view of U.S. Patent No. 5,916,596 to Desai et al.

Claims 1, 3-9, 12-18, 20-22, 24-29, 32, 33, 35-37, 40-48, 50-52, 54-59 and 62-71 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 6,277,391 to Seo et al. ("Seo") in view of U.S. Patent No. 5,916,596 to Desai et al. ("Desai"). Reconsideration and withdrawal of this ground of rejection is respectfully requested.

The present invention, as defined by independent claims 1 and 33, is directed, respectively, to a composition for local administration of anti-tumor chemotherapeutic to a patient and a corresponding method for local administration of anti-tumor chemotherapeutic to a patient. Each of claims 1 and 33 thus recites (1) a plurality of microspheres incorporating at least one anti-tumor chemotherapeutic and (2) a suspending solution comprising at least one apoptosis-inducing chemotherapeutic combined with an amount of a plasma protein effective in increasing the aqueous solubility of the apoptosis-inducing chemotherapeutic in the suspending solution. In certain preferred embodiments, both the anti-tumor chemotherapeutic and apoptosis-inducing chemotherapeutic are paclitaxel.

The Examiner correctly notes that Seo discloses paclitaxel-containing microspheres in a suspending liquid. Seo does not teach or suggest the presence in the suspending liquid, as

presently claimed, of at least one-apoptosis-inducing chemotherapeutic combined with an amount of a plasma protein effective in increasing the aqueous solubility of the apoptosis-inducing chemotherapeutic. The Examiner relies on Desai as teaching a liquid formulation comprising paclitaxel and a solubilizing plasma protein therefore. However, Desai does not teach or suggest, as presently claimed, that the liquid formulation also contains microspheres incorporating an anti-tumor chemotherapeutic. WO 99/13914 to Hegedus et al. ("Hegedus") has also been cited by the Examiner as teaching a paclitaxel-plasma protein complex. Hegedus is discussed on pp. 3-4 of the instant specification. However, Hegedus, like Desai, is deficient in failing to teach or suggest a suspension of microspheres incorporating anti-tumor chemotherapeutic in a solution of the paclitaxel-plasma protein complex.

It is respectfully submitted that there is absolutely no teaching or suggestion in the prior art of local administration of a composition to a patient, wherein the composition comprises both (1) a plurality of microspheres incorporating at least one anti-tumor chemotherapeutic and (2) a suspending solution comprising at least one apoptosis-inducing chemotherapeutic combined with an amount of a plasma protein effective in increasing the aqueous solubility of the apoptosis-inducing chemotherapeutic in the suspending solution.

As shown by the Examples in the instant specification, Applicants have discovered unexpected advantages attendant to local administration of the claimed composition. Example 1 shows that microspheres that have been intratumorally injected following an initial injection of a paclitaxel/human serum albumin (HSA) solution are more efficiently distributed within the tumor. Without being bound to theory, it is believed that the injection of the paclitaxel/HSA solution more effectively causes apoptosis throughout a larger percentage of the tumor volume, thus allowing better distribution of microspheres within the tumor. The significance of this Example is that achieving better intratumoral distribution of microspheres enables administration of chemotherapeutic agent from the microspheres to a larger tumor volume, resulting in improved treatment outcomes.

Indeed, Example 2 demonstrates that intratumoral injection of a paclitaxel microsphere-paclitaxel/HSA solution (Group Number IV) reduced human mammary tumor xenograft tumor size relative to intratumoral treatment with Taxol alone (Group Number III), and to a no-treatment control (Group No. I) and a saline control (Group No. II). The treatment effect was further enhanced when a paclitaxel/HSA solution was intratumorally injected prior to intratumoral injection of the paclitaxel microsphere-paclitaxel/HSA solution (Group No. V). These results demonstrate the non-obviousness of the valuable therapeutic advances of the claimed invention.

Rejection of claims 33, 35, 43, 54, 55 and 62-71 under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of U.S. Patent No. 6,569,459

Claims 33, 35, 43, 54, 55 and 62-71 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1-20 of U.S. Patent No. 6,569,459 ("the '459 patent"). Reconsideration and withdrawal of this ground of rejection is respectfully requested.

The Examiner states:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent 6,569,459 are generic to all the claims of the current application. That is, the claims of US Patent 6,569,459 fall entirely within the scope of the claims of the instant application, or, in other words, the claims of the US Patent 6,569,459 are anticipated by the claims of the instant application.
>
> More specifically, US Patent 6,569,459 teaches a method of administering paclitaxel comprising introducing a dose of paclitaxel, and an apoptosis inducing plasma protein. Claims 33, 35, 43, 54, 55 and 62-71 of the instant application claims a method for administration of an anti-tumor chemotherapeutic, paclitaxel, and an apoptosis inducing agent, a plasma protein. Although the

> claims of the instant invention teach the use of microspheres, the broad language of the US Patent does not prohibit the presence of microspheres.

Although it is not entirely clear, it appears that the Examiner considers the claims of the subject application to anticipate the claims of the '459 patent and, on this basis, concludes that the claims of the subject application and the '459 patent are not patentably distinct. It is respectfully submitted that the Examiner is incorrect that the claims of the subject application anticipate the claims of the '459 patent. Moreover, even if the claims of the subject application did anticipate the claims of the '459 patent (which they do not) this would not, without more, be a legally sufficient basis upon which the Examiner's obviousness-type double patenting rejection could be sustained.

The '459 patent and the subject application were filed on the same day. Therefore, the proper analysis requires the Examiner to consider whether any claim in the subject application is merely an obvious variation of any claim in the '459 patent. See MPEP §804.II.B.1.(a). Even if it were true that the rejected application claims are species falling within the scope of one or more of the '459 patent claims, this does not, *ipso facto*, mean that the application claims are mere obvious variants of the patent claims. Patents directed to species falling wholly within a prior art genus, even a prior art ***claimed*** genus, are issued regularly. The species need only be neither anticipated nor rendered obvious by the genus. Thus, if the application claims are species of a patented genus, the Examiner is required to base a conclusion of obviousness upon the usual factors, i.e., the scope and content of the patent claim relative to the claim in the application; the differences between the scope and content of the patent claim and the application claim; the level of ordinary skill in the art; and, any objective indicia of non-obviousness. See MPEP §804.II.B.1. The Examiner cannot simply conclude, without performing the proper inquiry, that the application claims are obvious variants of the patent claims. On the other hand, where the application claims are generic to the patent claims, obviousness-type double patenting will

typically be proper. In the present situation, the application claims are neither species of nor generic to the patent claims.

The claims of the '459 patent are directed to a method of administering paclitaxel to a patient having a tumor comprising a step of intratumorally injecting a paclitaxel formulation and a subsequent step of intravenously infusing paclitaxel into a patient. Thus, the claims of the '459 patent require two steps of providing paclitaxel, each step by a different mechanism, i.e., intratumoral injection and intravenous infusion. Claims 33, 35, 43, 54, 55 and 62-71 of the subject application require only a single step of locally administering an anti-tumor chemotherapeutic (which may be paclitaxel) to a tumor. Thus, the rejected claims of the subject application cannot anticipate any claim of the '459 patent. The fact that the claims of the subject application may embrace additional unclaimed steps is irrelevant.

Because the Examiner has premised the obviousness-type double patenting rejection upon both legally and factually incorrect premises, the rejection is improper and withdrawal thereof is respectfully requested.

Moreover, none of the rejected application claims is rendered obvious by any claim of the '459 patent. The application claims require the local administration to a tumor of microspheres incorporating an anti-tumor chemotherapeutic (which may be paclitaxel) in a suspending solution comprising at least one apoptosis-inducing chemotherapeutic (which may be paclitaxel) and a solubilizing plasma protein therefor. The claims of the '459 patent merely recite intratumoral administration of a formulation comprising paclitaxel and a solubilizing plasma protein.

The Examiner simply dismisses an essential element of the claimed invention, i.e., the presence, in the administered formulation, of microspheres incorporating an anti-tumor chemotherapeutic, by commenting that the "broad language of the US Patent does not prohibit the presence of microspheres." The fact that the claims of the '459 patent are broad enough to encompass microspheres is irrelevant to the proper analysis. The Examiner has failed to provide any reasoning as to why one of ordinary skill in the art would have modified the formulation

disclosed by the claims of the '459 patent to include therein microspheres incorporating paclitaxel. It is respectfully submitted that the claims of the '459 patent neither teach nor suggest, to a person having ordinary skill in the art, administering the paclitaxel/solubilizing protein formulation disclosed in the claims of the '459 patent having also suspended therein microspheres incorporating an anti-tumor chemotherapeutic and the unexpected benefits, as disclosed in the subject application, of administering the claimed formulation locally to a tumor.

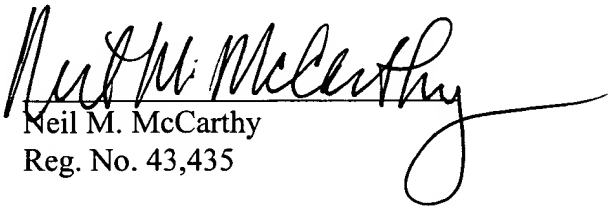
For this additional reason, reconsideration and withdrawal of the obviousness-type double patenting rejection based on the claims of the '459 patent is respectfully requested.

CONCLUSION

In view of the foregoing, it is respectfully submitted that this application is now in condition for allowance, which action is earnestly solicited. The Examiner is invited to contact the undersigned attorney to discuss any matter that would expedite allowance of this application.

The Commissioner is hereby authorized to charge any fees deemed necessary or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,



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